REMARKS

Reconsideration is requested.

Claims 1-4 and 6-10 are pending.

The Section 103 rejection of claims 1-4 and 6-10 over Jensen et al (WO 97/25044) in view of Palepu et al (U.S. Patent No. 4,963,551) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

The Examiner asserts the following:

> According to Jensen ICRF-187 has a low concentration in cerebrospinal fluid (page 9, line 24-28). So, the brain should have been exposed to some amount of ICRF-187 and this should provide some sensitization to radiation. See paragraph spanning pages 5-6 of the Office Action dated December 15, 2009.

The Examiner is referred once again to Figure 2B from the present application which shows clearly that there is no effect from combining dexrazoxane and radiation. Thus, even if the brain has been exposed to even a small amount of ICRF-187, there is clearly no sensitisation by this compound to radiation. If that were the case, the results obtained from a combination of dexrazoxane and radiation together would have been better than the results obtained from radiation alone. Figure 2B demonstrates that this is not the case.

The Examiner then goes on to say:

> Applicants have also admitted in the background section in the Specification (page 1, line 30 through page 2, line 2) that etoposide (the topoisomerase II poison) in combination with radiotherapy also results in synergistic cell kill. Id.

This is reflected in Figure 1B of the application where etoposide and radiation are shown to be slightly better in enhancing survival than either etoposide or radiation alone.

However, as can be seen from pages 18 and 19 of the application as filed, at the lowest concentrations of etoposide, the interaction between etoposide and radiation was antagonistic and synergism was only seen upon use of increasing concentrations of etoposide.

The Examiner concludes from the combination of the above two statements that:

> The combination of etoposide and radiation therapy should result in a synergistic effect. In addition to this any additional sensitization provided of the brain cells by the bisdioxypiperazine (ICRF-187) even though low in concentration, should have an additive effect. Id.

However, the Examiner is omitting to consider the third element in this combination, that is the effect of dexrazoxane and etoposide together. As can be seen both from Jensen et al and from Sehested et al (reference 17 in the application) ICRF-187 has an antagonistic effect on etoposide. In Jensen et al, the ICRF-187 is administered to protect non-tumourous tissue of the mammal against the toxic action of the etoposide. It is the etoposide alone which is responsible for killing the tumour cells.

In the Examiner's scenario, therefore, the ICRF-187 would not have an additive effect, but would rather have an antagonistic effect on the etoposide in the tumourous tissue, i.e. the brain.

It is also noted, as can be seen from page 19 of the application, that ICRF-187 did not affect etoposide up-take into the brain.

In conclusion, the present results show that:

(i) ICRF-187 and radiotherapy is no better than radiotherapy alone;

(ii) Etoposide and radiotherapy results in synergistic cell kill;

(iii) ICRF-187 did not affect the anti-cancer effect from etoposide alone;

however:

(iv) the combination of ICRF-187, etoposide and radiotherapy surprisingly extends the survival of test animals beyond that from the use of etoposide with either of ICRF-187 or radiation alone.

This surprising result could not have been foreseen from a combination of the disclosures of Jensen and Palepu, particularly given that the contribution of Palepu is only that ICRF-187 is a sensitiser to ionising radiation which, according to the results shown above, has been shown not to be the case in respect of brain tumours. Clearly if ICRF-187 were to sensitise brain tumours to radiation, the combination of ICRF-187 and radiotherapy would increase survival over the use of radiotherapy alone. The results of the present application show that this is not the case. Hence it cannot be argued that there could be any "additional sensitization provided of the brain cells by the bisdioxypiperazine" (see page 6 of the Office Action dated December 15, 2009) and there can be no "additive effect" (id.) of ICRF-187 on the etoposide and radiotherapy.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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